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Diogo Francisco Tomaz

The outcome of fungal infections in a Burn Intensive Care Unit: a study of 172 patients

As consequências de infeções fúngicas numa Unidade de Cuidados Intensivos de Queimados: um estudo com 172 pacientes

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Doutor Ricardo José Moreira Horta Oliveira

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Aos meus pais e irmã pelo cuidado, carinho e suporte. Aos meus amigos pelo apoio e incentivo.

Obrigado a todos.

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Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

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DESIGNAÇÃO DA ÁREA DO PROJECTO

Ciências médicas e da saúde

TÍTULO DISSERTAÇÃO

The outcome of fungal infections in a Burn Intensive Care Unit: a study of 172 patients

ORIENTADOR

Ricardo José Moreira Horta Oliveira

COORIENTADOR (se aplicável)

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☒
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	☐

Faculdade de Medicina da Universidade do Porto, 11/03/2019

Assinatura conforme cartão de identificação: Diogo Francisco Tomaz

Abstract

Background: Burned patients are a special fragile population in which infections are a leading cause of dead and morbidity. Fungal infections have become increasingly prevalent in Intensive Care Units (ICU) and burn ICUs. Management of fungal colonization and infection still constitutes a challenge for clinicians.

Aim: characterize the population of burn patients with fungal infections admitted in our Burn ICU.

Methods: a retrospective cross-sectional study of all patients admitted to a Burn ICU between 2013 and 2015. 172 patients were included and characterized regarding age, gender, date of admission and exit, type of burn, type of exit, burned Total Body Surface Area (TBSA) and presence of inhalation injury. Presence of fungal infection, causative pathogen and site of sampling were also registered. Statistical analysis centred around the presence of fungal infection was performed using IBM SPSS Statistics.

Results: 172 patients were included, 38 (22,1%) had a fungal infection and from this 8 (21,1%) died. Patients with fungal infection stayed more days than those without infection. However, this tendency didn't reach statistical significance when patients that died on ICU where excluded. No relations were found when comparing fungal infection with TBSA, burn aetiology, inhalation injury or mortality.

Conclusion: fungal infection are a major cause of morbidity and mortality despite of TBSA, burn type or presence of inhalation injury. Efforts should be made to improve management of fungal infections, especially on burn patients and other critically ill groups.

Keywords: burns; fungal infections; intensive care unit

Introduction

Infections are a worldwide health problem, with burned patients at a high risk of infection, due to their complexity and fragility. In critically ill patients, they constitute a major cause of morbidity and mortality.[1-3] In this group, infections are also a leading cause of dead and morbidity, being burn wound infection (BWI) a major public health problem and one of the most devastating traumas.[4-7]

Infections in burned patients are mainly caused by bacteria, followed by fungi and then viruses.[3] Due to the fungi ubiquity and the widespread antibiotic use, fungal infections have become an increasing problem over the past few years.[3-6,8-10] This type of infections account for approximately 20% of all infections in Intensive Care Units[1] (ICU), and in the burn patients scenario the situation is similar, representing 6-26% of infections according to some studies.[3,5-7,10,11]

This usually occur around or after the second week of burn injury, in patients who received or are taking antibiotics.[10] These infections are also known to be associated with inhalation injury and higher burned Total Body Surface Area (TBSA), as well as with diabetes or total parental nutrition (NTP) in severe burned patients.[5,6,8,11]

Despite some attention in the recent years, fungal infections still constitute a challenge in burned patients management, mainly due to delayed diagnosis and difficulties in fungi culture and its sensitivity[6,8-10], and have been described as contributors to burn wound progression.[3] Further than that, fungal infections are known to be associated to higher morbidity and mortality rates.[5,6,11] Although aggressive empiric treatment is not preconized, some authors defend it should be.[5]

The aim of this study was to determine the incidence of fungal infections in burned patients admitted in our Burn ICU between 2013 and the end of 2015 and to characterize this population.

Methods

2.1. Study Design

This is a cross sectional study, done retrospectively, regarding fungal infections on burned patients admitted to a Burn ICU.

2.2. Study setting

All patients admitted to the Centro Hospitalar São João (CHSJ) Burn ICU during the years 2013–2015 have been analysed. The CHSJ Burn ICU is one of the main burn units in Portugal and is associated with the Plastic and Reconstructive Surgery Department. All data was obtained from medical records retrieved retrospectively from paper records and a computerized, hospital-wide database, during the first trimester of 2019.

2.2. Assessment and management of burn patients

In our unit, the extent of burns is calculated by assessing the percentage of total body surface area (TBSA), according to the Lund and Browder chart. A patient admitted to the Burn ICU gets samples collected for microbiology analysis at the entrance moment. After this, every week during ICU stay blood cultures and urinary sample, skin swaps, skin biopsies or respiratory secretions are collected depending on infection suspicion by the clinicians.

Once blood culture results are obtained and resistance profile analysed, antibiotic or antifungal treatment is adjusted accordingly. The Burn ICU works in collaboration with a Group for Hospital Management of Infections and Treatment in order to define an appropriate treatment strategy.

2.3. Procedures

The study period was 3 years (2013-2015). Data of all patients admitted to the Burn ICU between this interval was retrieved, including age, gender and date of admission and exit, used for calculating the total time of stay in the Burn ICU.

Type of burn (6 different groups: “Fire”, “Chemical”, “Electrical”, “Scald burn” (“Hot fluids”), “Toxic skin syndromes” and “More than one”) and type of exit

from the Burn ICU (alive discharge vs death) were recorded. TBSA and Presence of inhalation injury were also registered.

Patients with a Toxic epidermal necrolysis (TEN) and other Toxic skin syndromes as well as the ones with multiple causes of burn were excluded from the analysis.

Regarding fungal infection patients who had at least one positive sample for fungal infection during their stay in the Burn ICU were identified. If a patient had more than one sample positive to fungal infection, only the first isolation was registered and used in the analysis.

Cause of infection was also registered in 6 groups (*Candida albicans*, *Candida non-albicans*, *Aspergillus spp.*, *Fusarium spp.*, *Zygomycetes* and Other or non-identified) and the source of the sample was as well registered and grouped (4 groups: Wound/Soft tissues, Urinary sample, Respiratory secretions, Blood culture).

2.4. Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics® version 23.0, with 0.05 as a significance level. T-test was used to identify differences in age, time of stay and TBSA according to the presence of fungal infection and to mortality. Qui-square or Fisher exact test were used to identify an association between the presence of fungal infection and the other qualitative variables. Mean and standard deviation were used for quantitative data, and absolute and relative frequencies for qualitative variables.

Results

3.1. Descriptive Data

Between 2013 and 2015, one hundred and seventy-eight (178) patients were admitted in the CHSJ Burn ICU unit. Of these, 172 patients were selected for this study, 116 (67,4%) were men and 56 (32,6%) women. (Figure 1). The mean patients age was 51.65 years, ranging from 12 to 94 years. (Table 1)

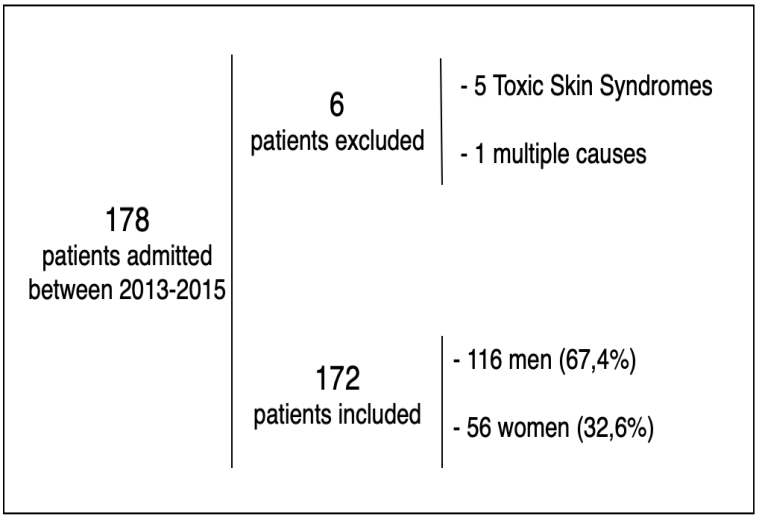

Figure 1 – Population Characteristics

The time of stay was in average 24 days (24,58 days) in the ICU. (Table 1). Forty-one (41 - 23,8%) patients had inhalation injury and 28 (16,3%) died in the Burn ICU. The most frequent cause of burn was fire (125 - 72,7%), followed by scald burns (17,4%), electrical burns (7%) and chemical (2,9%). (Figure 2) The mean TBSA was 23,18%.

Thirty-eight patients (22,1%) had a fungal infection in the Burn ICU, from which 21,1% (n=8) died. (Table 2)

Non-albican candidas were the most common isolated microorganisms in 20 patients (52,6%), followed *by candida albicans* (15 patients - 39,5%), *aspergillus spp.* (1 patient –

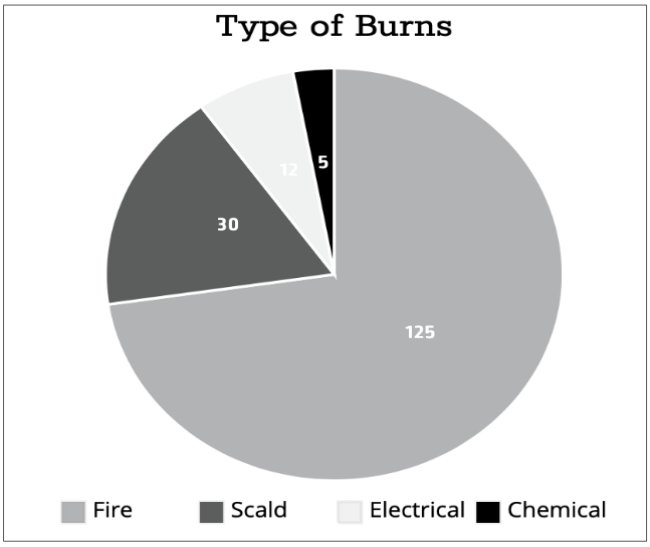

Figure 2 – Distribution according to Type of Burn

2.6%) and not identified agents (2 cases – 5.3%). Most fungi isolations were obtained from soft tissue samples (23 cases - 60,5%), followed by urinary samples (23,7%) and finally blood cultures and respiratory secretions samples (7,9% each) (Figure 3)

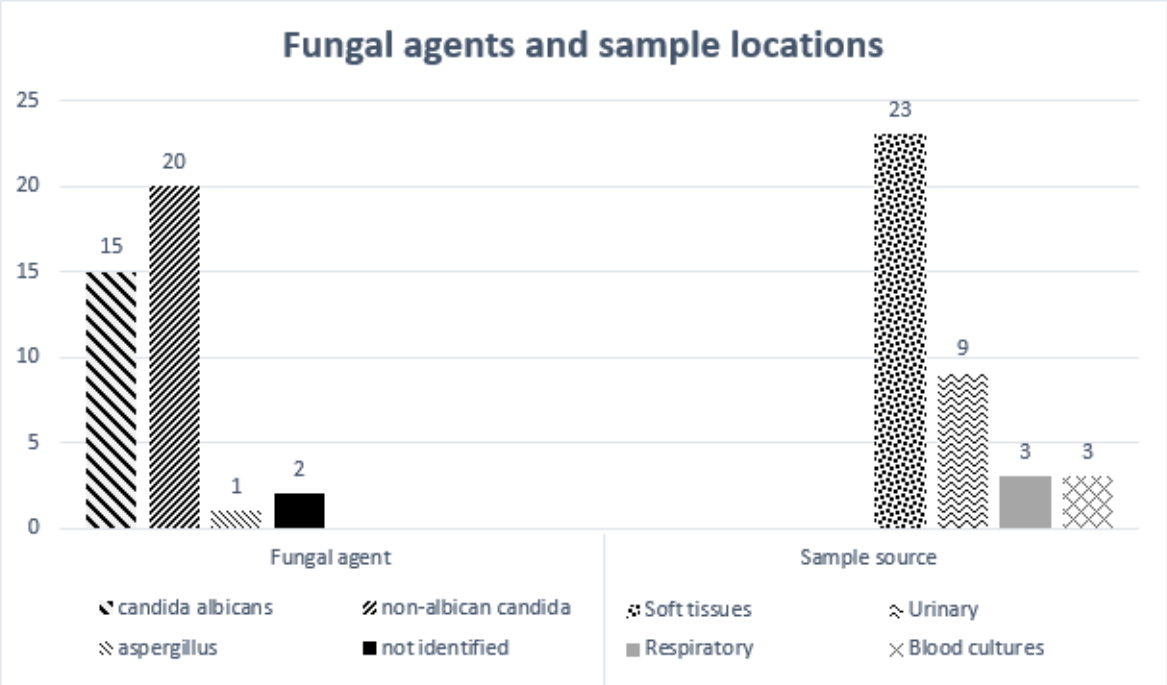

Figure 3 – Distribution of fungi infected patients according to fungal aetiological agent and to sample isolation source

3.1. Main Results

When comparing with patients with alive discharges from ICU, time of stay was less in the patients who died on ICU (15,04 vs 26,43, p=0,012), while age and TBSA were higher in this group (62,07years vs 49,62years and 57,26% vs 16,51%, respectively), all these results reaching statistical significance.

Was detected, with statistical significance, that the patients with fungal infection stayed more days than those without infection (32,76 vs 22,25 days, p=0,031). However, when patients that died on ICU were taken out of analysis, the analysis was short for statistical significance, despite being observed the same tendency (32,77 vs 24,76 days).

Regarding TBSA, there was no statistically significant differences between those with and without fungal infection. (Table 1)

	Total sample	Fungal Infection			Mortality		
		with	without	p value	Death	Discharge	p value
Age (years)							
Mean	51,65	55,74	50,49	0,152	62,07	49,62	**0,002**
SD	19,94	21,51	19,40		20,68	19,22	
Time of Stay							
Mean	24,58	32,76	22,25	**0,031**	15,04	26,43	**0,012**
SD	21,95	27,27	19,70		26,20	20,63	
Time of Stay (excluding patients dead on ICU)							
Mean	26,43	32,77	24,76	0,058	---	26,43	---
SD	20,63	22,84	19,77			20,63	
TBSA							
Mean	23,18	23,58	23,06	0,905	57,26	16,51	**<0,001**
SD	23,23	22,17	23,61		30,46	14,01	

Table 1 – Relation of Fungal Infection and Mortality with age, time of stay (total and excluding dead patients) and TBSA.

Comparing the patients with fungal infection with those without, we didn't find any statistically significant differences regarding mortality or the presence of inhalation injury. However, a tendency for higher mortality was seen on those patients with fungal infection (21,1% vs 14,9%).

Similarly, no differences between groups were found when aetiology of burn or TBSA categories were analysed. Fire burns were the most common type in both groups, and the TBSA groups distribution was similar regardless of presence of fungal infection. (Table 2)

		Total		Presence of Fungal Infection				
				with		without		
		n	%	n	%	n	%	p value
Fungal Infection	Yes	38	(22,1%)					
	No	134	(77,9%)					
Mortality	Discharged	144	(83,7%)	30	(78,9%)	114	(85,1%)	0,366
	Death	28	(16,3%)	8	(21,1%)	20	(14,9%)	
Inhalation Injury	No inhalation injury	131	(76,2%)	29	(76,3%)	102	(76,1%)	0,980
	Inhalation injury	41	(23,8%)	9	(23,7%)	32	(23,9%)	
Aetiology of Burn	Fire	125	(72,7%)	29	(76,3%)	96	(71,6%)	0,784
	Electricity	12	(7,0%)	1	(2,6%)	11	(8,2%)	
	Chemical	5	(2,9%)	1	(2,6%)	4	(3,0%)	
	Scald	30	(17,4%)	7	(18,4%)	23	(17,2%)	
TBSA (categories)	< 30%	122	(70,9%)	28	(73,7%)	94	(70,1%)	0,635
	30 - 59%	25	(14,5%)	4	(10,5%)	21	(15,7%)	
	≥ 60%	18	(10,5%)	5	(13,2%)	13	(9,7%)	
	missing	7	(4,1%)	1	(2,6%)	6	(4,5%)	

Table 2 – Relation of Fungal Infection with mortality, inhalation injury, aetiology of burn and TBSA categories.

Discussion

Extensive thermal injury, seen in burned patients admitted in an Intensive Care Unit, results in severe cardiovascular, end-organ perfusion and immune derangement, known as Burn Shock. These patients exhibit a clinical picture marked by systemic inflammation, described as systemic inflammatory response syndrome (SIRS), mostly caused by the tissue damaged by the burn. This is associated with burn induced immunosuppression which facilitates pathogens colonization and infection.[12,13] Infection may lead to sepsis, a major cause of morbidity and also mortality, accounting for the majority of deaths in burn patients.[4-7,12-15]

Burn wounds provide an optimal environment for bacterial growth, due to deficient perfusion and nutrient rich conditions. Normally, colonization ensues by environment, gut and oropharyngeal track pathogens, being gram positive bacteria the first to colonize followed by gram negative bacteria, colonization by fungi usually occurs later on.[2,12]

The incidence of fungal infections was of 22.1%, which is similar to other studies around the world with incidences ranging from 26% to 44% [5,6,9-11], but contrasting with the other works with incidence ranging from 6% to 10%, including a multicentre American Burn Association review (ABA)[8,16]

Fungal infection have become increasingly prevalent following broad-spectrum antimicrobial use and given the ubiquity of fungi and fragility of burned patients.[4,6,8,10,12,13] Most frequently, fungi come from environment as burn patients roll on the floor to extinguish flames, use current water to wash chemical and fire burns and use contaminated bandaging left open on air. Other environmental foci described are air conditioning vents and floor drains. Often infection arises from the patient's own flora.[12]

Fungal infections are associated with high morbidity and mortality rates in burned patients, regardless of TBSA inhalation injury or age as described in other works.[2,4,9-12] Despite this we didn't find a statistically significant between fungal infection and mortality.

This study detected, with statistical significance, a higher time of stay among the patients with fungal infection, such relation is also seen in other studies.[7,8,11] When patients death on ICU were taken out of analysis this relation didn't reach statistical significance. The timing of infection by fungi may explain this, as some studies have shown that fungal infection commonly appear after 2 - 4 weeks of hospitalization[2,5,6,10], patients who died short after admission in ICU might not have the time to get infected by fungi.

Most commonly, according to some literature, fungi isolation are obtained from wound/soft tissues samples, followed by urinary samples and respiratory secretions and lastly from blood cultures, this pattern meets our findings regarding sample sites[11,16] We also find *candida spp*. to be the most common pathogens causing fungal infection, which was also reported in multiple studies[5,6,8,10,13]

Some studies described an association of TBSA with fungal infection, with mainly TBSA between 30% and 60% being associated with higher fungal infections rate.[5,6,10,11] Our findings don't support this association, with no statistically significant relation being found between fungal infection and TBSA (either normal and grouped).

The management of fungal infections presents as a challenge. The diagnostic of fungi colonization and infection isn't easy as routine culture techniques require around 7 to 14 days and venous blood culture sometimes fail to reflect the fungal agent. This leads to a delay in treatment initiation and complicates fungal infection management.[6,10,12] Antifungal treatment itself is difficulted by toxicities and limited treatment options. Fluconazole is the most common antifungal agent, other azoles, amphotericin B and echinocandins are other options. Wound closure with autographs and early burned tissue debridement remain the most successful treatment options.[4,11,12]

Although this study includes a database of 172 patients, a bigger population could have been used, expanding the time of study, that could reveal other findings that our study fell short in demonstrating. Temporal recording of fungal infection diagnosis on the Burn ICU would have shown some interesting data regarding fungal infections timing on hospitalized patients. Moreover, more

variables as treatment agent and patients risk factors (e.g. diabetes mellitus, heart failure, autoimmune diseases, etc.) that weren't analysed because of lack of data may be important to better understand and characterize fungal infections in burned patients.

Conclusions

Despite not reaching statistical significance as in other works, a tendency for higher mortality among patients with fungal infections was seen. Fungal infections didn't seem to be related to TBSA, burn type or presence of inhalation injury. Diagnosis and treatment of fungal infections have a lot of setbacks that difficult approach to this important problem,

This emphasizes the need for better tools (either on early diagnosis and treatment agents) for fungal infection management, especially in critically ill groups as the burn patients, as it represents a high burden problem in this group.

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Legends

Figure 1 – Population Characteristics

Figure 2 – Distribution according to Type of Burn

Figure 3 – Distribution of fungi infected patients according to fungal aetiological agent and to sample isolation source

Table 1 – Relation of Fungal Infection and Mortality with age, time of stay (total and excluding dead patients) and TBSA.

Table 2 – Relation of Fungal Infection with mortality, inhalation injury, aetiology of burn and TBSA categories.

	Total sample	Fungal Infection			Mortality		
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Table 2 – Relation of Fungal Infection with mortality, inhalation injury, aetiology of burn and TBSA categories.

ANEXOS

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A Theory section should extend, not repeat, the background to the article already dealt with in the Introduction and lay the foundation for further work. In contrast, a Calculation section represents a practical development from a theoretical basis.

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Results should be clear and concise.

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The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

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If there is more than one appendix, they should be identified as A, B, etc. Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

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List funding sources in this standard way to facilitate compliance to funder's requirements:

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Declaração

Para os devidos efeitos se declara que Diogo Francisco Tomaz entregou o projecto *"Fungal infections in burned ICU patients"*, e que o mesmo foi submetido para avaliação à Comissão de Ética para a Saúde do Centro Hospitalar Universitário de São João/FMUP em 15 de Fevereiro de 2019, tendo sido este protocolo aprovado nesta mesma reunião.

Porto, 20 de Março de 2019

O Secretário da Comissão de Ética